REMARKS

This Amendment is submitted in response to the February 23, 2006 Office Action, wherein the Examiner rejected claims 1- 27. By this Amendment, claims 1, 5, 19, 20, and 21 have been amended. Upon entry of this Amendment, claims 1-27 will be pending and in condition for allowance. Reconsideration of the application in view of the Amendments proposed herein is respectfully requested, in view of the following remarks.

Prior to addressing the issues raised by the Office Action, Applicants take this opportunity to set forth the following brief remarks in connection with their invention, which relates to a particularly versatile, stable, and compact pharmaceutical formulation for use in the treatment of helminthiasis of mammals, and particularly tapeworm, hookworm, roundworm and heartworm of domestic animals and farm animals. The present invention also provides a method of treating helminthiasis in mammals, which comprises administering to the mammal in need thereof, an anthelmintically effective amount of a pharmaceutical formulation of the invention.

As discussed in the application, applicants determined that it is particularly desirable to provide a formulation containing an avermectin such as ivermectin. However, this is difficult, because ivermectin tends to degrade other anthelmintics. Thus, anthelmintic formulations including ivermectin tend to be relatively dilute, so as to isolate the ivermectin with excessive filler or solvent. Consequently, anthelmintics including ivermectin have tended to comprise relatively low percentages of active components, often to levels as low as 10-15 % or less. On the other hand, compositions in accordance with the invention can comprise 30%, 40% and even over 50% actives, because the ivermectin has been isolated with a relatively small amount o

material to form a composition in accordance with the invention, with a method discussed in the application.

The present invention accordingly provides a composition and a method for preparing a pharmaceutical formulation containing ivermectin and a method and composition that can contain ivermectin plus other active compositions such as hexahydropyrazinoisoquinolines and anthelmintic pyrimidines such as tetrahydropyrimidines and benzimidazoles. Examples of these include praziquantel, pyrantel, and febantel, respectively. One preferred method involves isolating the ivermectin through spray granulation with inert polyethylene glycol or cellulose, which preserves the active ingredients without the need for additional anti-oxidents or stabilizers or excessive filler material.

Provisional Obviousness-type Double Patenting Rejection

On page 2 of the February 23, 2006 Office Action, claims 1-27 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1 - 27 of copending Application No. 10/637,807 in view of Mihalik (U.S. Patent No. 6,340,672). The Examiner acknowledged that the claims were different due the addition of benzimidazole to the presently claimed formulation but alleged that a person would have been motivated to add benzimadizole to the anthelmintic formulations claimed in the application in view of Mihalik (column 3, lines 16-32).[1]

In response, in an attempt to advance the prosecution of the subject application, but without conceding either the correctness of the Examiner's position or the need to file a Terminal

[1] Applicants note that while the current application contemplates the addition of benzimidazole, the citation to Mihalik indicates a differently spelled compound, benzimadizole.

Disclaimer, Applicants enclose herewith a Terminal Disclaimer with respect to U.S. Patent Application No. 10/637,807 and in accordance with 37 C.F.R. 1.321(c).

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 5 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. Specifically, the Examiner alleged that there is not antecedent basis in claim 1 for the term "pyrimidine" in claim 5.

Claim 1 has been amended (in a broadening manner) to reflect the proper class designation for the pyrimidine. Chaim 5 is amended to refer to tetrahydropyrimidines, a narrower class of anthalmintic pyrimidines (claim 1). With the amendment, claim 1 now provides the proper antecedent for claim 5. The application [Paragraph 005] states that the invention relates to "a pharmaceutical formulation containing ... anthelmintic pyrimidines such as tetrahydropyrimidines." Therefore these changes do not introduce any new matter. Thus the amendments to claims 1, 5 are fully supported in the application as originally-filed and the rejection shall be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Initially, the applicants note that the combination in claim 1 is now amended to specify a solid formulation, which is supported by the specification and Example 1-4. Claim 1 is further amended to describe that the particles of ivermectin are covered with polyethylene glycol or cellulose as a result of a spray granulation process.

The Examiner rejected claims 1 – 19 and 25-27 under 35 U.S.C. 103(a) as being unpatentable over Mihalik (U.S. Patent No. 6,340,672) ("Mihalik"). Specifically, the Examiner alleged that Mihalik "discloses a parasitical formulation comprising avermectin and further teaches that additional parasiticidal agents ... may also be used in the formulation (column 3 lines 16-32). Thus the Examiner concluded that a person of ordinary skill in the art would be motivated to combine multiple parasiticial agents because such a person would have expected the resulting formulation to be useful antiparasitic formulation and such combination is therefore prima facie obvious over Mihalik. Applicants respectfully traverse the rejection.

Applicants respectfully submits that Mihalik does not render the present invention obvious. It is not obvious to a person of ordinary skill in the art to select tetrahydropyrimidine, hexahydropyrazinoisoquinoline and avermectin out of the 28 parasiticidal agents listed in Mihalik. As stated in the application, this particular combination of anthelmintics has been determined by the inventors to be particularly preferred for fighting a wide variety of organisms. Nothing in Mihalik suggests that a combination of the agents in claim 1 would be therapeutically beneficial, among the millions of possible combinations of agents.

Moreover, claims 1, 20, and 21 have been amended to specify the use of a polyethylene glycol or a cellulose material to encapsulate the active agents. Even if those skilled in the art were motivated to combine avermectin, hyxahydropyrazinoisoquinoline, and tetrahydropyrimidine they must still overcome the problem with active anthelmintic ingredients degrading each other in a combination, especially in a solid form, as described generally in paragraph 0003 and 0004 of the specification.

Ivermectin is a potent antiparasitic agent as disclosed in U.S. Pat. No. 4,199,569. However, it is difficult to use in combination with other anthelmintic compounds. Specifically, it is shown that ivermectin has a compatibility problem with the presence of the two other anthelmentic agents: pyrantel (pamoate) and praziquantel, even though a solid combination of these compounds is therapeutically desirable (Declaration ¶ 3). Experimental results showed that ivermectin degraded by about 10% after three weeks when directly combined with other anthelmintic compounds. (Declaration ¶ 4, 5).

In contrast, Mihalik merely teaches that a combination of anthelmintics would be soluble in a pyrrolidone solvent system. It does not discuss the stability issue or resolve the known difficulty of stabilizing ivermectin over time or preventing ivermectin degradation in the presence of other active anthelmintic compounds. Accordingly, it is not obvious for a person skilled in the art to create a stable solid formulation combining the multiple anthelmintics based on the liquid formulation in Mihalik (Declaration ¶ 7). Moreover, with the addition of the "solid form" limitation, the amended claim 1 no longer includes any liquid based formulation disclosed by Mihalik.

The Examiner rejected claims 20-24 under 35 U.S.C. 103(a) as being unpatentable over Mihalik in combination with Maxfield et al (U.S. Patent No. 4,597,969) ("Maxfield"). The Examiner alleged that since Maxfield discloses spray drying into granules (column 5, lines 3) – 32) such anthelmintic agents as ivermectin (column 1, lines 10 – 15) in order to stabilize unstable drugs, a person having ordinary skill in the art would have been motivated to "spray dry ivermectin disclosed by Mihalik into granules in order to stabilize said compound."

Applicants note that claims 1, 20, and 21 now specifically disclose the use of polyethylene glycol or cellulose for covering the ivermectin particles as a result of the spray granulation process, which was not disclosed in the prior art. The method for spray granulating the unstable ivermectin particles and the resultant formulation are supported by paragraph 0027, 0028, and 0029. Examples 1 and 2 further demonstrate the use of polyethylene glycol while Examples 3 and 4 support the use of cellulose. In claim 19, the term "comprising" has been amended to "consisting essentially of."

Applicants respectfully disagree with the Examiner's rejection, in light of the new amendments. As stated previously and in paragraph 0003 of the application, it is very difficult to prepare a solid ivermectin composition. To solve this problem, the present invention discloses a spray granulation process with a polyethylene glycol or cellulose carrier material that unexpectedly enhances the stability of the undesirably unstable ivermectin without having to rely on excessive stabilizer or filler material.

As discussed in the previous response, Maxfield actually teaches away from the invention, because it shows that the stabilizing effect is confined to a combination of alginic acid and magnesium hydroxide over a narrow range of concentrations. Beyond this combination the stability of ivermectin drops. Clearly the cited prior art requires the presence of filler materials or stabilizers such as alginic acid and magnesium hydroxide. Thus, a person skilled in the art, upon reading Maxfield, would not have thought to spray granulate ivermectin with polyethylene glycol or cellulose (which achieves unexpected stability without requiring the addition of alginic acid, antioxicants, or other stabilizers) (Declaration ¶ 8). Therefore, it would <u>not</u> be obvious for Applicants to achieve the desired stability with less filler material by eliminating such a major component of the Maxfield formulations.

Furthermore, claimed carriers are inert to the other active ingredients. In contrast, alginic acid is not a pharmaceutically desirable additive. The use of alginic acid in the method disclosed by Maxfield will actually reduce the effectiveness of the combination. Alginic acid, being negatively charged, can bind to positively charged compound, including the active compound pyrantel, and thus impact the bioavailability of the resultant combination (Declaration ¶ 9). Thus the use of polyethylene glycol in the present invention enables a simpler formulation that reduces the risk of deleterious reactions or interactions occurring between the carrier and the anthelmintic ingredients (Declaration ¶ 9).

Applicants maintain that the claimed invention is patentable for the reasons set forth above. Accordingly, Applicants respectfully request that these rejections be withdrawn.

CONCLUSION

If any issue is raised which would delay the allowance of the application, the Examiner is respectfully requested to telephone the undersigned in an effort to resolve any outstanding issues. No fee, other than the $130.00 Declaration filing fee, is deemed necessary in connection with the filing of this Communication. However, if any other fee is due the amount of such fee may be charged to Deposit Account No. 19-4709.

Respectfully submitted,

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